New and Improved Tools

Discovery and development of new drugs, vaccines and diagnostics for the TDR target diseases, under Product Research and Development, is an area that has expanded in recent years. New and improved tools for use in infectious disease prevention and control — drugs, vaccines, diagnostics, epidemiological tools, environmental tools — are being developed. The progress indicators include new candidates (drugs, vaccines, diagnostics) ready to enter the development pipeline; new candidates in development; new and/or improved tools (drugs, vaccines, diagnostics) resulting in regulatory approval; and new and/or improved epidemiological tools developed for use in control of neglected tropical diseases.
NEW CANDIDATES READY TO ENTER INTO DEVELOPMENT

Drug discovery research

The major changes in Drug Discovery Research in 1999 and 2000 were the updating and restructuring of the screening operations; the progression of candidates for treatment of some target diseases into initial pharmacokinetic studies and, in some cases, further development; an increased emphasis on natural product research; and the preparations to include tuberculosis and possibly dengue in the drug discovery portfolio.

Under the new screening system, compounds submitted for integrated screening are first tested in a single laboratory for activity in vitro against a range of different parasites. If a compound is active, it is sent for more detailed analysis to one or more laboratories that are specialized in individual parasitic diseases. This has resulted in increased throughput and efficiency of the screening operations.

In the natural products area, several projects investigating the activity of purified antimalarial or anti-leishmanial compounds, or semi-synthetic analogues, are being funded (see below). As part of a broader effort to enhance research capability strengthening in disease endemic countries, a meeting on Natural Products for Treatment of Tropical Diseases was organized in August 2000, to address issues of common interest for both traditional and pharmaceutical medicine disciplines and to seek ways in which effective, safe and cheap natural products may be more easily developed.

In malaria drug discovery research, the principal current development candidates are synthetic antimalarial peroxides, several of which have been analysed in detail in pharmacokinetic studies. Further development work on one series of peroxides is now being funded by the Medicines for Malaria Venture (MMV). In the future, it is foreseen that other promising malaria projects which have been nurtured in TDR might also be taken up by MMV. Work on two other peroxide series has produced molecules with improved physical and pharmacokinetic properties, as discussed at a TDR-organized meeting on these candidates in September 2000. Selected molecules from one series are being characterized further. Additional research on identified molecular targets or relevant biochemical pathways (defined kinase families, dihydrofolate reductase, shikimate pathway, choline uptake and metabolism) continues to be supported, and analogues of manzamine and dioncophylline, natural products with interesting antimalarial activity, are being characterized. At the screening level, an important step forward was the successful launch of the JPMW – a partnership between 12 Japanese pharmaceutical companies, the Japanese Ministry of Health and Welfare, and TDR/WHO – in October 1999. Under this agreement, it is planned to screen some 12 000 compounds and natural product extracts for antimalarial activity over a five-year period. Some compounds with good activity in vitro and reasonable activity in animal models have been identified and characterized, and, in most cases, analogues of these compounds are being tested or will soon be available for testing.

For onchocerciasis and lymphatic filariasis, moxidectin was established as the leading candidate for further development. At the discovery level, new approaches to target validation and lead discovery have been introduced. Research using gene knockout and RNA inhibition approaches to target validation is being funded, as are two molecular target screens that were set up following a TDR-organized meeting in 1998 on Molecular Targets for Filariasis. The traditional screening on whole organisms has been reorganized and now incorporates initial in vitro studies on cultured parasites. A meeting on Wolbachia bacteria as possible targets for anti-onchocercal drugs1, 2 (December 1999) led to the testing of a series of antibiotics, some of which show promising anti-onchocercal activity and are being investigated further. Work on possible mechanisms of resistance to ivermectin led to the establishment of a programme to develop diagnostic tools for the detection of drug resistant onchocerciasis.

The standard current treatments for visceral leishmaniasis, and also treatment with miltefosine (an oral treatment under development for visceral leishmaniasis), require multiple administrations of the drug and correspondingly long treatment courses. A natural product with good anti-leishmanial activity after a single injection in animal models, PX 6318, is being progressed through pharmacokinetic and toxicological studies, and would significantly shorten treatment times if successful. Other projects being funded at the basic research level include studies of

pyrophosphate metabolism as a possible drug target in *Leishmania*, and mechanisms of parasite resistance to arsenical anti-leishmanial drugs.

The search for new molecules with activity against African trypanosomiasis continued. As was discussed at a TDR-funded meeting on ‘New drugs for kinetoplastid diseases’ (Heidelberg, 1999), there is a lack of validated targets and corresponding leads for developing drugs against the trypanosomiases and leishmaniases. It has been especially difficult to identify molecules that combine good activity, lack of toxicity, and ability to cross the blood-brain barrier, all necessary attributes of a drug that is to be effective against sleeping sickness caused by chronic infection with African trypanosomes. Two series of active molecules were investigated in chronic infection models in some detail. A development candidate from the most promising series (amidine derivatives) is now being progressed at the preclinical level with additional financial support from the Gates Foundation. Additional TDR-funded work includes the identification of new leads based on their ability to inhibit trypanothione reductase, one of the few validated trypanosomal target molecules.

New molecules continued to be screened for activity in animal models of Chagas disease, with interest focused on possible treatments for the chronic form of the disease. Some anti-fungal azoles showed good activity in animal models of infection, and one of these, posaconazole (SCH 56592), is currently considered an excellent candidate for progression into human clinical trials.

Tuberculosis and dengue were recently introduced into the TDR disease portfolio. The Drug Discovery Research unit is now funding some initial TB screening work, and, in partnership with the Global Alliance for TB Drug Research and Development, has plans to expand this to the screening of more selected libraries, including natural product-based ones. TDR also commissioned a consultant report to assess if chemotherapy is a viable option for dengue, or whether the initial research should focus more on diagnostics or vaccines (successful treatment for dengue haemorrhagic fever is likely to be very dependent on rapid, accurate diagnosis of the disease).

Vaccine discovery research

Significant progress was made during 1999-2000 in the area of vaccine discovery research, leading to new development candidates for vaccines for malaria, leishmaniasis, and schistosomiasis. Supported were:

- Research projects on pre-erythrocytic and asexual blood stage antigens for *Plasmodium falciparum* and *P. vivax* malaria, based on recombinant proteins, synthetic peptides and deoxyribonucleic acid (DNA) plasmids.

- Long-term research projects on transmission-blocking vaccines, aimed at preventing the successful development of the malaria parasite in its mosquito host. Although the development and eventual deployment of transmission-blocking vaccines is feasible, there is little commercial interest in these vaccines and development is proceeding slowly. The need to develop safe and effective transmission-blocking vaccine candidates to the stage of ‘proof of principle’ in order to induce industrial commitment to vaccine production was identified as being urgent by an international group of experts at a meeting, sponsored by the World Health Organization (WHO)/TDR, Roll Back Malaria (RBM), the Gates Malaria Vaccine Initiative (MVI), and the US National Institutes of Health (NIAID and Fogarty International Centre), in December 1999.

- Studies aimed at identifying promising second generation recombinant protein antigens as candidates for an effective leishmanial vaccine – especially needed for combating visceral leishmaniasis.

- Research and evaluation in large animals (sheep, pigs, cattle, water buffalo) of promising candidate antigens and adjuvants for a vaccine against schistosomiasis japonicum, a disease found in China and the Philippines. If successful at reducing the *S. japonicum* reservoir in veterinary
use, the same candidate vaccine antigens would be evaluated for use as a vaccine in humans. Vaccine research and development for tuberculosis and dengue is currently being addressed by the Health Technology and Pharmaceuticals cluster (Vaccine Development Unit) of WHO. Progress in TDR’s contributions to new vaccines for TB and dengue will be carried out under the umbrella of the new Initiative for Vaccine Research (IVR) within WHO. TDR, as part of this IVR initiative, organized the second bi-annual meeting on Novel Adjuvants Currently in Clinical Testing at the Fondation Mérieux, France. This meeting provides an excellent opportunity for research scientists and pharmaceutical companies to exchange information and evaluate progress in this rapidly evolving field.

Diagnostic discovery research

Ivermectin resistance has developed in parasites (worms) of veterinary importance and there is a fear this may happen with *Onchocerca volvulus*. For this reason, TDR has established a product development team to develop a sensitive polymerase chain reaction (PCR)-based assay for detecting ivermectin resistance in *O. volvulus*.

The team is focusing on genetic evaluation of material from adult *O. volvulus* recovered from nodules obtained from naive patients or patients treated with ivermectin at the Onchocerciasis Clinical Research Centre in Hohoe, Ghana. A genomic library of *O. volvulus* has been constructed and restriction fragment length polymorphism (RFLP) analysis performed on seven relevant genes, certain of which appear to be selected. In another approach, based on genetic analysis of candidate ivermectin resistance genes from *Haemonchus contortus/H. placei* crosses, several genes have similarly been excluded.

To expand this work, arrangements have been made with the Onchocerciasis Control Programme of West Africa to provide the investigators with *O. volvulus* material from areas with different exposures to ivermectin. A method is being developed for immobilizing DNA on filter paper and subsequently utilizing it for two to three rounds of multiplex PCR from a single *O. volvulus* microfilarial larva (L3 stage) under the conditions of higher humidity likely to be encountered in the field.

NEW CANDIDATES IN DEVELOPMENT

Drug development

MALARIA

Rectal artesunate

Survival of a severe malaria patient depends on the speed of obtaining chemotherapy. To survive, such a patient must access a health facility where injectable treatment can be given immediately and safely. If no treatment is given, the disease is fatal. A drug to replace injectable treatment would capture the population at highest risk of death from malaria at a point in the evolution of the disease that provides the greatest potential for reducing the risk of complications and death. There is, at present, no drug that meets these requirements. Such a compound would need to be quickly bioavailable, of high efficacy and safety, and of stable formulation for the tropical areas where malaria is transmitted. Once the patient is able to reach an equipped health facility, a more precise diagnosis can be made and follow-up treatment administered as required.

TDR is completing submission of a regulatory dossier for rectal artesunate to the US Food and Drug Administration, the UK Medicines Control
Agency, and the Swiss Inter Cantonal Office for the Control of Medicines, for registration of the drug under a new indication for malaria: emergency treatment of acute disease where a patient is unable to take drugs by mouth and unable to access injectable treatment. WHO is the applicant for registration and the dossier is currently under review by the three agencies. Stability and bioequivalence data, to be submitted in May 2001, will complete the dossier for registration of the product. Plans for how best to launch the product in malaria endemic countries are being prepared jointly by TDR and Roll Back Malaria.

Partner:  
• GlaxoSmithKline

Malarone

Acute malaria in pregnancy is associated with higher than normal mortality and increased risk of spontaneous abortion, especially in non-immune mothers. In semi-immune individuals, it is associated with low birth weight, the most important risk factor for infant mortality. Although women of childbearing age living in endemic areas acquire partial immunity to malaria, which protects them against the acute disease, this protection is lost or lowered during pregnancy due to the immuno-suppression that follows conception. To protect pregnant women against malaria complications, the most effective treatment with the lowest possible risk of clinical failure is recommended.

There are increasing reports of chloroquine (CQ) and sulphadoxine-pyrimethamine (SP) resistant falciparum malaria from most parts of Africa. In south-east Asian countries, particularly Thailand, CQ and SP are now almost ineffective and their use is limited. Thus there is an urgent need to search for alternative drugs that can be used in areas where there is chloroquine resistance and substantial SP resistance, or in situations where SP is contraindicated. It was the increasing resistance to SP, currently promoted for intermittent treatment during pregnancy, that gave rise to the original idea for developing Malarone as a treatment in pregnancy.

Malarone is a fixed-dose combination of 250mg atovaquone and 100mg proguanil hydrochloride per tablet, and is considered a possible alternative to CQ and SP. The drug is now available in more than 30 countries (including the United States, Canada, countries in Europe, Africa, Asia, the Middle East, Latin America) for the treatment of acute, uncomplicated falciparum malaria. Clinical studies have demonstrated excellent safety and tolerance compared to other standard antimalarial regimens such as mefloquine and quinine/tetracycline. While in excess of 200 000 courses of atovaquone/proguanil have been prescribed worldwide, only 122 adverse events have been reported in post-marketing surveillance, suggesting that the drug is well tolerated. However, although Malarone has been shown to be safe in children and adult malaria patients, its safety in pregnancy has not yet been established.

In planning for a Phase IV clinical trial in pregnant women, the toxicological profiles of atovaquone and proguanil, in particular the reproductive toxicology, were reviewed by an independent panel of expert consultants. The panel concluded that the available safety data, which address the two drugs – atovaquone and proguanil – separately, are adequate to support investigations into the potential use of Malarone for the treatment and prevention of malaria in pregnancy.

However, physiological changes during pregnancy such as delayed gastric emptying, decreased motility of the gastrointestinal tract, increased volume of fluid, and increased proteins, may induce significant change in drug pharmacokinetics, particularly as in the case of atovaquone, which has high plasma protein binding capacity (greater than 99%). In addition, drug metabolism can significantly change during pregnancy. With no pharmacokinetic data of atovaquone in pregnant women yet available, conducting a pharmacokinetic study in pregnant patients will provide first-hand information on the pharmacokinetics, efficacy and safety of Malarone prior to the conduct of large-scale trials. However, such a study in this population requires extreme caution.

The primary objective of the study is to investigate the pharmacokinetics of Malarone in pregnancy, allowing for possible racial and geographical variations. The trial is being conducted at two independent sites, one in Zambia (sub-Saharan Africa) and the other in Thailand (south-east Asia), with the purpose of gathering preliminary information for future larger trials of Malarone in acute uncomplicated malaria in pregnant women. The following studies are proposed:

1. Pharmacokinetic study on symptomatic patients (small group)
2. Symptomatic treatment (large group)
3. Intermittent treatment (large group)

The ideal treatment should be very effective, with the lowest possible risk of adverse effects and the highest probability of killing all asexual stages in the blood and placenta.
Pyronaridine/artesunate

An oral fixed ratio combination product containing pyronaridine and artesunate is being developed for the treatment of uncomplicated malaria in Africa and Asia. This combination is seen as a safe, effective, and relatively low-cost replacement for the oral antimalarials commonly used for treatment of uncomplicated malaria, but to which resistance has developed in certain areas. Current data indicate that pyronaridine, when used as a single agent, is effective in cases of chloroquine resistance and is satisfactorily tolerated. But the addition of artesunate to pyronaridine will create an even better treatment for falciparum malaria because it is likely that the artemisinin derivative will: decrease fever and parasite clearance time when compared to the use of pyronaridine as a single agent; prevent the development of resistance; and possibly lower the rate of malaria transmission. There is already good evidence from three small Chinese clinical trials that the addition of an artemisinin derivative to pyronaridine is safe, very effective and well tolerated. Shin Poong Pharmaceutical Co. Ltd. and TDR, via a memorandum of understanding agreement, have already initiated jointly funded preclinical toxicology studies with the two compounds, and plan to study use of the combination in humans beginning in early 2002.

Chlorproguanil/dapsone

The chlorproguanil/dapsone development project, for the treatment of uncomplicated falciparum malaria in Africa, is nearing completion. Large, blinded, comparative, multicentre Phase III clinical trials, designed to determine the safety and efficacy of a three-day regimen of chlorproguanil/dapsone, were completed in early 2001 and the data are now being analysed. Submission of the regulatory dossier to the UK Medicines Control Agency and African national regulatory agencies will begin in September/October of 2001. Chlorproguanil/dapsone is active against African SP-resistant falciparum strains and has a much shorter plasma half-life than SP, so a low propensity to select resistant parasites. It is seen as an alternative or replacement for SP. Chlorproguanil/dapsone will be made available to the public sector of African countries at a preferential price of <US$0.50 per adult treatment course. In March 2001, WHO, TDR, Roll Back Malaria, WHO/Essential Drugs and Medicines, the WHO Regional Office for Africa, and the University of Liverpool, inaugurated a Chlorproguanil/dapsone Access Group which will explore mechanisms by which chlorproguanil/dapsone can be equitably accessed by African populations and review evidence gathered to assist national control programmes in making policy decisions concerning their use of chlorproguanil/dapsone.

Chlorproguanil/dapsone/artesunate

Studies using a fixed ratio combination of chlorproguanil/dapsone with artesunate (under the acronym CDA) for the treatment of uncomplicated falciparum malaria in Africa have recently been initiated. Chlorproguanil/dapsone combination is seen as safe, effective, and low cost (see above), while the potent compound artesunate is a semi-synthetic derivative of artemisinin, derived from a Chinese plant. The advantages of adding an artemisinin derivative to chlorproguanil/dapsone are three fold: faster fever and parasite clearance times; reduced rate of development of resistance; and possibly decreased malaria transmission due to the gametocidal effects of artesunate. Preclinical toxicology citing studies are under way and the team anticipates that CDA will be used in humans in the third quarter of 2001.

Fosmidomycin

As a phosphonic acid derivative, fosmidomycin represents a novel class of antimalarials which work through inhibiting the 1-deoxy-D-xylulose 5-phosphate (DOXP) pathway. Hence, activity against multidrug-resistant strains of *P. falciparum* may be anticipated. Previously investigated as an antibacterial agent in the 1980s, early promise of the drug for treatment of uncomplicated urinary tract infections was countered by the relative lack of activity against recurrent infections. Nevertheless, the drug was well tolerated even at high doses.

More recently, Jomaa et al have identified activity in experimental models of malaria and against the target parasite in vitro. In collaboration with Jomaa Pharmaka, TDR has contributed to the design of a proof of principle study in which the response to a seven-day therapeutic regi-
men will be evaluated in 30 subjects with acute uncomplicated falciparum malaria enrolled at centres in Gabon, Tanzania and Thailand, commencing in January 2001.

It is expected that the results from this study, on which future strategies will be determined, will be available in June 2001.

**TUBERCULOSIS**

*Streamlining the development and registration of new drugs*

Throughout 2000, TDR worked with the Rockefeller Foundation and other agencies to establish the Global Alliance for TB Drug Development, launched by the Director-General of WHO in Bangkok, October 2000. The goal of the Alliance is to bring to registration, by 2010, at least one new agent for tuberculosis (TB) which will make treatment of TB substantially shorter, will be effective against multidrug resistant TB, and/or will be effective in the treatment of latent TB infection.

TDR initiated dialogue with national regulatory agencies (NRAs) in order to standardize guidelines for the registration of new chemical entities effective against TB and of the new four-drug fixed-dose combinations. A meeting of NRAs was convened with industry representatives in September 2000 at which NRA representatives agreed to the proposed guidelines and to lobby for their formal adoption by their respective agencies.

An analysis of the compounds in early development as anti-TB agents within the public domain was carried out by TDR and revised by a meeting of experts in December 2000. The resulting document will provide essential data on the most promising compounds in the discovery, preclinical and clinical phases of development.

Funds have been sought to expand TDR’s existing screening activities to include TB. TDR is in discussion with Aventis, the manufacturer of rifapentine, for joint development of rifapentine to the point of determining its proper role in TB control in low income countries. The possibility of partnerships with manufacturers of the most useful looking fluoroquinolones, especially Bayer Ltd for moxifloxacin, will be explored, while dialogue with Chiron on the nitroimidazopyranos will continue.

*Activities for streamlining registration of four-drug fixed-dose anti-TB combinations*

The development and regulatory approval of new drugs for the treatment of TB is one of the cornerstones of effective TB control and a process of paramount importance to each country for protecting the health of its citizens. But it is a time-consuming process and current regulations are a disincentive to industry. Therefore, TDR and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) are leading measures to streamline the process of developing and registering new chemical entities and four-drug fixed-ratio combinations – as recommended through the WHO essential drug list – for TB. The development of a standardized regulatory policy framework was discussed at a TDR sponsored meeting in September 2000, to which representatives from developed and developing country national regulatory agencies, other government agencies, the pharmaceutical industry, and academic establishments, were invited.

It is TDR’s intention to: (i) develop a single harmonized guideline to guide all actors (industry, international regulators, public health institutions, individual scientists) in the development of new anti-TB agents; (ii) enhance the efficiency and speed of registering new anti-TB agents; (iii) incorporate ‘state-of-the-art’ science, e.g. surrogate markers, in the clinical development of new TB drugs; and (iv) develop a single international harmonized approach for the registration of fixed-dose combinations of four anti-TB drugs. The national regulatory authorities of 22 high burden TB endemic countries and all members of the International Committee on Harmonisation (ICH) will provide input to proposed guidelines on regulatory harmonization which, it is hoped, will be finalized by the end of 2003.

**ONCHOCERCIASIS and LYMPHATIC FILARIASIS**

Two types of drug are described for treatment of onchocerciasis and lymphatic filariasis:
- microfilaricides, which kill immature worms.
- macrofilaricides, which kill adult worms.

Existing microfilaricides are effective, but there is no suitable macrofilaricide currently available. Because treatment with microfilaricides must be...
maintained for a number of years, in fact for the length of life of the adult worm in the human host (more than 10 years in the case of onchocerciasis), a suitable, safe and effective macrofilaricide would allow more impact to be made on controlling filarial diseases than is currently possible using microfilaricidal treatment.

**Albendazole combinations**

TDR, through its network of clinical researchers, is supporting studies to evaluate albendazole in combination with either ivermectin or levamisole as potential macrofilaricidal treatment for *O. volvulus* patients, and albendazole co-administered with either ivermectin or diethylcarbamazine (DEC) for treatment of lymphatic filariasis patients.

The studies in onchocerciasis patients are being conducted at the Onchocerciasis Clinical Research Center in Hohoe, Ghana. The effects of single-dose co-administration of ivermectin (Mectizan) with albendazole, of albendazole with levamisole, or of ivermectin with levamisole, are being evaluated, the primary endpoints being safety, pharmacokinetics and effect on microfilaria and macrofilaria. Preliminary results suggest that, although safe, none of the combinations is more effective on adult worms than ivermectin alone. Also, so far, no pharmacokinetic drug interactions have been detected.

The studies in lymphatic filariasis patients are being conducted in light of the WHO/SmithKlineBeecham (now GlaxoSmithKline)/Merck recommendations on use of co-administration of albendazole with ivermectin or DEC for elimination of lymphatic filariasis. Three studies are in progress:

- **On the Island of Pemba, Tanzania**, a randomized, double blind study in 1000 subjects is under way to compare single-dose ivermectin + albendazole with single-dose ivermectin alone. This study will define: a) unacceptable adverse drug reactions occurring within 7 days of treatment; b) the proportion of microfilaria positive subjects that, one year after treatment, remain microfilaria negative – the primary endpoints being 80% reduction in prevalence for ivermectin alone and 90% reduction in prevalence for albendazole + ivermectin. As secondary end-points, the study will assess: a) prevalence of microfilaremic subjects 3 and 6 months after treatment, and reduction in microfilaraemia 3 and 6 months after treatment; b) the cure rate (proportion of patients with clearance of eggs from stools) of *Trichuris trichiura* (human whipworm) infections 21 days after treatment, and reduction in the *T. trichiura* egg count 21 days after treatment compared to before treatment; c) cure of other soil transmitted helminths. The results are expected during the 3rd quarter 2002.

- **In Alleppey, India**, a study in lymphatic filariasis infected vs. uninfected individuals is under way to evaluate the pharmacokinetic profiles of albendazole and DEC when administered as single drugs or when co-administered as in lymphatic filariasis elimination programmes. Besides assessing safety and laboratory parameters, this study will, for the first time, determine if there is any adverse pharmacokinetic drug interaction. Determination of drug plasma levels will be carried out at the University of Iowa, US. Results of the study are expected to be available during the 4th quarter of 2001.

- **In Wardha, India**, a study in 1347 subjects is ongoing to assess the safety, tolerability, efficacy and population pharmacokinetics of DEC co-administered with albendazole as compared to DEC administered alone. The primary end-points will be information on the number of patients without microfilaraemia at 3, 6 and 12 months after treatment, and on the clinical
signs and symptoms and adverse events in the two arms of the study. The results are expected to be available during the 4th quarter 2002.

LEISHMANIASIS

**Miltefosine**

Miltefosine, an anticancer drug that TDR and ASTA Medica (now Zentaris) have been developing for visceral leishmaniasis, could be the first oral treatment to become available for this disease (see TDR Programme Report, 1997-1998). During the biennium, Phase II (dose-finding) and Phase III (efficacy confirmation) trials in adult patients were successfully completed. In mid-2001, the drug will be submitted for registration in India and Germany for use in patients aged over 12 years. As well, a Phase II trial in children was completed, and a Phase III trial in children has begun (expected to finish end of October 2001), an indication which could later be added to the criteria for use. A Phase IV (post registration, in a real field situation) trial has been planned for India, Nepal and Bangladesh, which will feed into the control programme. This Phase IV trial will be supported by the WHO Regional Office for South-East Asia and the Government of India.

**Paromomycin**

Further development of this compound is currently on hold due to lack of funding, but it is hoped it can be re-activated during the 2002/3 biennium.

SCHISTOSOMIASIS

**Artemether**

Chemotherapy using praziquantel has been the cornerstone of schistosomiasis control for more than 20 years. As yet, there is no proof for the emergence of drug resistance, but rapid re-infection is a problem. Artemether, a drug developed for malaria, has been found to interfere with the development of adult schistosome worms after infection, and would conceivably stop morbidity, which is induced by granulomatous effects against eggs not excreted from the host. However, long-term use of artemether would not be financially feasible and it is advised not to use it on a large scale in malarious areas because of the risk of drug resistance. On the other hand, there are large malaria-free areas in China, South America and North Africa where artemether could be useful as an adjunct to elimination of schistosomiasis as a public health problem. TDR is currently involved in field studies to resolve these questions.

AFRICAN TRYPANOSOMIASIS

Each of the drugs currently in use for African trypanosomiasis has its drawbacks. Pentamidine and suramin, used only for early-stage disease, both have adverse side effects. Of the two drugs used for late-stage disease, melarsoprol has serious adverse effects which leads to fatal outcome in 1-5% of patients, while eflornithine, which treats only the gambiense form of the disease, has been out of production. No oral treatment exists.

A project to discover novel compounds with activity against late-stage disease, using animal models and supported at the Shanghai Institute of Pharmaceutical Industry, has been terminated following the lead compound’s (SIPI 1029) failure to cure late-stage infection in the vervet monkey model of African trypanosomiasis at Kenya Trypanosomiasis Research Institute (KETRI), Nairobi. For the same reason, another lead compound – the diamidine CGP 40215 – has been dropped from the development portfolio.

Companies are donating key drugs for sleeping sickness, funds for drug development, and funds for disease management and control.
**Eflornithine**

Eflornithine was discovered in 1980 by Dr Cyrus Bacchi through a TDR-supported study on polyamine metabolism in trypanosomes. Known as the ‘resurrection drug’ because of its spectacular effect on comatose patients in late-stage gambiense sleeping sickness, eflornithine is well tolerated in patients. However, there are two problems with its availability: first, it has been out of production since 1995, and second, it is expensive.

In 1999, the remaining available stocks of the drug were donated for treatment of sleeping sickness by Hoechst Marion Roussel (now Aventis). These stocks are projected to last until June 2001. Also, in December 1999, this company granted WHO the production rights for eflornithine in order that a third party manufacturer could be found. Some eight pharmaceutical companies were identified by WHO and Médecins sans Frontières (MSF) as potential manufacturers. In November 2000, WHO and MSF approached Bristol-Myers Squibb (BMS), USA (which, with Gillette, has recently introduced Vaniqa™, an eflornithine cream marketed for reducing growth of facial hair in women), for help in finding a source of bulk material that could be formulated into injectable form before the available stocks run out in June 2001. Subsequently, in February 2001, BMS announced that it would donate 60,000 doses of eflornithine annually for three years, starting in June 2001, for use in treatment of sleeping sickness. However, this development was overtaken in May 2001 by an agreement signed between WHO and Aventis, by which Aventis will donate US$25 million to support WHO’s activities in the field of African trypanosomiasis for a five year period. The donation comprises: a donation of three key drugs, pentamidine, melarsoprol and eflornithine, and funds for disease management and control and research. Out of the Aventis annual donation of US$5 million, US$750,000 will go to TDR as a designated fund for drug development, focusing on oral eflornithine, development of a new route of synthesis for eflornithine, and development of existing molecules for future treatment. BMS has agreed to fund production of the bulk material for 60,000 doses of eflornithine for the first year and also to provide 140kg of oral eflornithine for Phase III clinical trials.

Several approaches to reducing the cost of eflornithine have been considered by TDR in the past. One approach was to look at synthesizing eflornithine by a new route, but this was put on hold due to lack of funds. It will now be reactivated. Another approach was to compare 14-day treatment with 7-day treatment, as reported in the TDR Programme Report for 1997-1998, which showed the 7-day regimen to be significantly less effective than the 14-day regimen for new cases although, for relapsed patients, the 7-day treatment is as effective as the 14-day treatment and can be recommended. Another approach being followed is based on use of an oral formulation of the drug, which would not only be much less expensive than the i.v. formulation, but also much easier to administer. Pharmacokinetic studies on oral eflornithine, in which two oral doses are being compared for efficacy and safety, are in progress in Côte d’Ivoire. If the results are satisfactory, Phase III multicentre clinical trials will start in 2002, according to good clinical practice (GCP).

Another approach to improving availability concerns the use of drug combinations. There is experimental evidence for synergism between eflornithine and melarsoprol, and clinical trials involving combinations of these two drugs could be envisaged.

**Vaccine development**

**MALARIA**

Significant progress has been made over the last biennium with respect to the development and clinical evaluation of promising candidate vaccines for malaria, and specifically, vaccines for *P. falciparum* malaria, the cause of over one million deaths annually, mainly in children under five in Africa. In general during the biennium, TDR played a catalytic and facilitative role in the various vaccine development programmes described below. The vaccine candidates target different antigens from different stages in the life cycle of the malaria parasite.

*Pre-erythrocytic vaccine candidates*

These are designed to prevent the parasite’s infective sporozoite stage from entering or developing within liver cells of an individual bitten by an infected mosquito.
FIFTEENTH PROGRAMME REPORT

Partners:
• Institut de Biochimie, U. de Lausanne
• Dictagene, Suisse
• SEDAC, Lille

CS-102 plus Montanide ISA 102

The circumsporozoite protein (CS), comprised of a central repeat region and two flanking domains, has been well characterized in murine malaria models and human malarias. CS-102 is a 102 amino acid synthetic peptide segment of the C-terminal region of the *P. falciparum* CS protein (amino acids 282-383) shown to be highly immunogenic in mice and monkeys. A homologous peptide from *P. berghei* conferred protection against sporozoite challenge in mice, and preclinical studies using sera and lymphocytes from Africans living in malaria endemic areas demonstrated that B, CD4+ and CD8+ epitopes (particular sites on antigens to which particular antibodies bind) are recognized in the 102 amino acid sequence. An initial Phase I trial conducted in Lausanne, Switzerland, has provided promising results for safety and immunogenicity and, when sufficient good manufacturing practice (GMP) grade peptide becomes available, additional Phase I/II trials are planned for Europe prior to evaluating the vaccine candidate in Africa.

Partners:
• GlaxoSmithKline Biologicals
• Walter Reed Army Institute for Research
• Medical Research Council, The Gambia

RTS,S plus SBAS2

RTS,S is a leading vaccine candidate comprised of the *P. falciparum* circumsporozoite coat protein co-expressed with hepatitis B coat protein particles and formulated with a novel adjuvant SBAS2. This promising version of a pre-erythrocytic malaria vaccine has evolved from extensive preclinical and clinical studies over the years, conducted in collaboration with the Walter Reed Army Institute in Washington, DC, and the Armed Forces Research Institute of Medical Sciences (AFRIMS) in Bangkok, Thailand. Initial Phase I/II clinical studies with a mosquito challenge showed over 80% protection; however, the duration of this protection appears to be limited to several months only. Subsequent Phase II field studies conducted in The Gambia have confirmed these findings in semi-immune adult volunteers. TDR's input to date has consisted mainly of provision of independent monitoring and review of the project. Currently plans are under way to conduct de-escalation studies in children in The Gambia, using lyophilized RTS,S antigen mixed with the SBAS2 adjuvant at the time of injection. The Malaria Vaccine Initiative has recently agreed to provide major financial support to GlaxoSmithKline (GSK) Biologicals for taking this project forward.

Asexual blood stage vaccine candidates

Vaccines which target these stages of the malaria parasite prevent it from entering or developing in red blood cells.

Partners:
• The CRC for Vaccine Technology, Walter and Eliza Hall Institute of Medical Research (WEHI)/ Queensland Institute of Medical Research (QIMR)/ LaTrobe University
• IMR-PNG Vaccine Solutions
• Biotech Australia

AMA-1 plus Montanide ISA 720

The merozoite apical membrane antigen (AMA-1) represents a leading asexual blood stage vaccine under development in Australia and Papua New Guinea with TDR support. In extensive preclinical studies, AMA-1 has been shown to provide partial protection in rodent and monkey malaria models and to produce high titres of growth inhibitory antibodies when tested in vitro. The current *P. falciparum* version under development by TDR is a recombinant protein expressed in *E. coli* and formulated with the adjuvant Montanide ISA 720. An initial Phase I study in Brisbane, Australia, demonstrated safety but low immunogenicity, likely due to loss of potency. The current focus is on the reproducible production of adequate amounts of GMP clinical grade material for additional Phase I/II trials in Australia and Papua New Guinea.

Partners:
• The CRC for Vaccine Technology, WEHI/ QIMR/LaTrobe University
• IMR/PNG Vaccine Solutions
• Biotech Australia

Combination B plus Montanide ISA 720

Combination B consists of a mixture of three *P. falciparum* merozoite and ring stage-derived recombinant protein antigens (MSP-1/MSP-2/RESA) formulated with Montanide ISA 720 as adjuvant. Clinical studies successfully completed to date include Phase I and Phase II studies in Brisbane, Australia, and Phase I/II studies in Papua New Guinea in children 5-10 years old. A significant reduction in parasite densities was observed in a recent Papua New Guinea Phase II field study, with a 47% efficacy against the 3D7 allele of MSP-2, suggesting that MSP-2 was an active component of the vaccine. The current focus is on production of sufficient quantities of clinical grade materials to conduct Phase III efficacy studies. TDR's input to date has consisted mainly of provision of independent monitoring and review of the project.
**EBA 175 plus adjuvant TBD**

Erythrocyte Binding Antigen-175 (EBA-175) is a sialic acid binding protein from *P. falciparum* that serves as a ligand for the parasite to bind to the red blood cell with subsequent junction formation leading to invasion. TDR is supporting the development of Region II, a functional binding domain of EBA-175. Rabbit antibodies raised against the pure, functionally active PfF2 region II antigen have been shown to block the binding of erythrocytes and to inhibit parasite growth in erythrocyte cultures in vitro. The methods used to produce the recombinant protein in *E. coli* are currently being scaled up at the International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi, India, for use in the production of clinical grade PfF2 for use in Phase I trials. Monkey studies aimed at the identification of a suitable adjuvant for formulation with EBA-175 are under way in collaboration with the Malaria Vaccine Institute in Cali, Colombia.

**MSP-1-19 plus alum**

The major merozoite surface protein-1 (MSP-1) represents the leading asexual blood stage vaccine candidate to date. The 200 kDa MSP-1 precursor undergoes proteolytic processing to yield a series of peptides including a membrane-bound 42 kDa C-terminal moiety. This MSP-1.42 fragment is further cleaved to yield the MSP-1.19 candidate antigen. Several of these MSP-1 candidate antigens have been shown to provide protection in various murine and monkey malaria model systems, and multiple versions of the MSP-1.19 antigen are under development globally. A homologous version of the *P. cynomolgi* MSP-1.19, together with CFA as adjuvant, provided solid protection in the naturally occurring malaria model in TDR-sponsored Toque monkey studies conducted in Sri Lanka. TDR is currently supporting development by the Institut Pasteur of a MSP-1.19 C-terminal version of the *P. falciparum* antigen expressed in baculovirus and initially formulated with alum as adjuvant.

**MSP-1.42 plus QS-21**

As mentioned above, the merozoite-derived MSP-1 is a leading asexual blood stage candidate antigen and up to 12 different versions of candidate recombinant proteins expressed in *E. coli*, yeast, baculovirus and transgenic mouse milk, as well as synthetic peptides, are under development globally. TDR is currently funding the development of a synthetic gene version of the *P. falciparum* MSP-1.42 molecule using insect cell codon composition and not containing a hexa-his tag. A conventional purification scheme has been worked out for the baculovirus-expressed protein, with a satisfactory recovery of purified protein exhibiting the required folding and functional activity. Two novel adjuvants (QS-21 and Montanide ISA 51) have provided promising protection results when tested in challenge studies in *Aotus* monkey experiments conducted in Hawaii. Current activities are focused on the scale up and production of clinical grade MSP-1.42 to be used in Phase I trials in the USA.

**LEISHMANIASIS**

The first trial of a vaccine against visceral leishmaniasis in humans was completed. The trial was conducted by scientists of the Institute of Endemic Diseases, University of Khartoum, Sudan, supported by TDR and assisted by Médecins sans Frontières-Holland, using a vaccine composed of autoclaved *Leishmania major* promastigotes (Fesharki et al at Razi Vaccine and Serum Institute, Iran) mixed with a low dose of bacillus Calmette-Guérin (BCG) (as adjuvant), which was compared with BCG alone. The presence of extensive cross-reactivity between different species of *Leishmania* was the rationale behind this trial of a vaccine, made from *L. major* which had proved almost 100% effective in langur monkeys against *L. donovani* infection.

The trial was carried out in the Sudan where visceral leishmaniasis is a major cause of morbidity and mortality (a prevalence of 80-130 per 1000 in the study area). Here, as in many other endemic countries, the development of a safe, effective and cheap vaccine would be a long-term solution for controlling visceral leishmaniasis. Drug treatment does exist, but is prohibitively expensive, not easy to administer, not always available, and resistance to it develops rapidly. Vector control is also a possibility, but requires infrastructure that is not available.

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**Results of the first trial of a vaccine against visceral leishmaniasis showed it to be associated with a lower incidence of disease.**

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In the double-blind study, no evidence was found that two injections of Leishmania + BCG offered significant protective immunity against visceral leishmaniasis compared with BCG alone. However, the Leishmania + BCG vaccine did induce significantly higher rates of leishmanin skin test (LST) conversion (30%, vs. 7% by BCG alone) at 42 days, which was associated with a significantly lower incidence of disease – responders had a 43% lower incidence of leishmaniasis as compared to LST non-responders (7.2% vs. 12.7%, p<.003). Similar results, i.e. lower incidence of disease in LST converted than non-converted individuals, have been obtained in other studies. As BCG alone might have some protective activity against leishmaniasis, as seen in the therapeutic trials of Convit et al in Venezuela, the real prophylactic effect of the vaccine, compared to no vaccine (and not to BCG as in this trial), might be higher. In this trial, BCG was used for ease of keeping the trial blind.

To improve the immunogenicity of killed Leishmania vaccines, different adjuvants used in humans are being sought. Safety and efficacy trials of alum-precipitated Leishmania + BCG have begun in the Sudan. Preliminary results showed that a single injection produces a dramatic immune response – a strong LST conversion – in every recipient (better than three injections without alum). Multiple doses of L. major + BCG vaccine did not prove to be more effective than a single injection in preventing cutaneous leishmaniasis, so development of this vaccine is not being pursued without the addition of alum. Following a successful comparative safety and immunogenicity trial of different formulations of Mayrink’s vaccine (killed L. amazonensis, produced by Biobras, Brazil), with or without adjuvant, a trial of three injections without adjuvant has begun in Colombia (Velez ID, Universidad de Antioquia, Medellin).

A dozen or so recombinant antigens were recently evaluated as potential second generation vaccine candidates in independent testing coordinated by TDR and conducted in two laboratories in Brazil and Denmark. Unfortunately the results were inconclusive, as not all the control preparations were active. Several second generation vaccines (synthetic peptides and multi-fusion recombinant proteins) are being developed outside TDR, and efforts are being made to create a collaborative programme for these activities, ideally through a consortium which will coordinate the definition, testing and advanced development of promising candidate antigens.

SCHISTOSOMIASIS

There has been some progress in the field of schistosome vaccine development, both in strategic research on the basic immunological mechanisms and in practical field work. In searching for a vaccine, reduction of reinfection without stimulation of the egg-associated granuloma reaction is sought, rather than complete immunity. In this case, transmission would likely not be fully interrupted and natural infection could be counted on to boost vaccine-induced protection. Since schistosomes do not replicate in the human host, even a partially effective vaccine would have a role in control, while the combination of chemotherapy followed by vaccination promises to be an effective intervention with long-term effect. There is evidence that people living in endemic
areas naturally acquire immunity against schistosomiasis, supporting the notion that it should be possible to protect by vaccination against infection and morbidity.

Currently TDR is monitoring two Phase II human field trials, in Senegal and Niger, on a *S. haematobium* glutathione-S-transferase (GST) vaccine candidate developed in France. Results are expected in 2003.

The Schistosomiasis Vaccine Development Programme (SVDP), based in Egypt and supported by USAID, is planning to scale up GMP production and carry out human field trials with an invertebrate muscular protein paramyosin. Another vaccine candidate, a synthetic peptide construct containing multiple antigen epitopes (MAP) of the schistosome triose phosphatase isomerase (TPI), is also being supported but has not reached the same level of development. Sm14, a fatty acid-binding *S. mansoni* antigen, is a Brazilian vaccine candidate which has also reached the scale-up stage. This is of particular interest since it shares protective epitopes with *Fasciola*, another zoonotic liver fluke which infects humans. All these activities are being followed by TDR.

TDR is also sponsoring developmental vaccine work with regard to *S. japonicum* which, apart from limited foci in Laos and Indonesia, is only found in China and the Philippines. Several antigens are at the stage of clinical testing in cattle, pigs and water buffalo, experimental hosts which might reflect the situation in man. A veterinary product could have a positive transmission-blocking effect for human populations.

**Diagnostics development**

**TUBERCULOSIS**

Successful implementation of the WHO strategy for tuberculosis control (DOTS) depends upon the detection and treatment of infectious TB cases. The inability to do this quickly and with certainty is one of the primary impediments to improved disease control. Sputum microscopy, the primary diagnostic tool available in most areas of the world, is cumbersome, insensitive, and gives no information about antimicrobial resistance. The poor performance of TB diagnostic tests leaves large numbers of patients undetected, erodes faith in public health services, impedes the expansion of DOTS, increases morbidity, and allows continued transmission of disease. The pandemic of human immunodeficiency virus (HIV) has made this difficult situation much worse.

Rapid, simple, inexpensive and sensitive TB diagnostic tests are urgently needed for (in order of priority) case detection, drug susceptibility determination, and identification of latent infection. Recently, impressive technical advances, including simplified immunoassay formats, superior reagent preparations, improved understanding of mycobacterial biology, and availability of the complete *M. tuberculosis* genome sequence, have brightened the prospect for diagnostic product development for TB. Harvesting this technical progress to create new diagnostic tools appropriate for low-income settings is the mandate of the TB Diagnostic Initiative. This TDR Initiative has been working with a network of partners in industry, academic research, non-governmental organizations, and public health to facilitate the development, testing, approval, and use of improved diagnostic tools to assist in TB control efforts.

A range of tests are now under development including:

- Nucleic acid amplification and hybridization.
- Phage replication.
- Antibody detection.
- Novel culture methods.
- Cellular immune response detection.
- Antigen detection.
- Physicochemical detection.

Trials in humans of *S. haematobium* and *S. mansoni* vaccine candidates are ongoing or about to begin, while several candidate antigens for an *S. japonicum* vaccine have reached the stage of clinical testing in animals.

The TB sputum test is cumbersome and insensitive.

The TB diagnostics initiative was established to stimulate and facilitate industry to develop a rapid and simple serologic test for tuberculosis. A range of tests are currently under development.
These tools are being developed primarily by large and small biotechnology companies, often with close academic collaboration. The role of TDR has been to facilitate commercial development by removing intellectual, technical and logistic barriers to TB diagnostic R&D.

SCHISTOSOMIASIS

The greatest problem related to schistosomiasis is the development of morbidity, which is a slow process that varies between individual patients. Most people have only minor signs of infection but as many as 20 million are seriously ill. TDR has contributed to the development of a standardized procedure for gauging pathology due to schistosomiasis using ultrasound. This technique can be used for all types of morbidity including female genital schistosomiasis which is an important, yet neglected, feature of the disease. TDR has taken the lead in promoting research on forms of schistosomiasis after transmission has ceased because, even if the disease is eradicated, morbidity from it will continue. For example, in spite of eradication of the disease in Japan more than 25 years ago, there are still many patients in the country with morbidity due to schistosomiasis.

Ultrasonography has become an invaluable extension of the clinical investigation of patients with schistosomiasis as it provides direct evidence of the pathological changes associated with the infection. The manual published by TDR in 200011 was developed through various draft stages separated by experience in use of the technique. It is expected that a final meeting will be needed to finalize work on the manual, which began in Cairo in 1990. This final meeting, tentatively planned for 2002, will focus on schistosomiasis (caused by *S. japonicum*) in the Far East but will allow adjustments to be made with respect to examination of patients with *S. mansoni* and *S. haematobium* infections, if necessary.

Ultrasound provides direct evidence of the pathological changes associated with schistosomiasis. An updated practical guide to use of the technique has been produced.

\[11\] Ultrasound in schistosomiasis: A practical guide to the standardized use of ultrasonography for assessment of schistosomiasis-related morbidity. Document no. TDR/STR/SCH/00.1 available from TDR on request and to download at: www.who.int/tdr/publications/publications/ultrasound.htm

Ultrasound can be a valuable tool in investigations of schistosomiasis patients.
NEW AND IMPROVED TOOLS RECEIVING REGULATORY APPROVAL

MALARIAS: Artemotil treatment

Artemotil has been under development by TDR and partners since 1991. During the biennium, clinical development of the compound was completed and the final parts of the clinical dossier were submitted to the Dutch regulatory authorities. On 22 May 2000, the Dutch registration authorities approved two artemotil products (in sesame oil) for the treatment of severe *P. falciparum* malaria by intramuscular injection.

Artemotil (previously known as β-arteether, see Figure 1) is a semi-synthetic derivative of artemisinin, a compound first isolated by Chinese scientists from the plant *Artemisia annua* in 1972, since when a number of derivatives have been developed and registered and have entered use in a variety of countries. Artemotil is the ethyl ether of dihydroartemisinin and is active against all blood schizont stages of *P. falciparum*, including the very early ring forms. It is the first artemisinin derivative to be registered as a single entity according to European standards, and is indicated for patients with severe malaria. Until now the only possibility for treatment of severe malaria, according to European standards, was through intravenous quinine, which currently remains the drug of choice in most parts of the world, despite its sometimes serious adverse effects.

Clinical studies in patients with severe malaria were carried out first in adults, and later in children who could not be treated with oral medication, or who had critical cerebral malaria, in Africa and Thailand. Administration is by intramuscular injection over three days and is restricted to hospitals. No serious or inconvenient side-effects were reported during clinical trials. The drug represents an excellent alternative to quinine, over which it has clear advantages: it causes a swifter decrease in parasite numbers; is simpler to apply; has far fewer undesirable side-effects. Artemotil also has advantages in cases where the patient is not able to retain food (and thus cannot be treated with oral medication).

Now that artemotil is registered in the Netherlands, a programme to extend regulatory approvals to disease endemic countries is to be initiated. If initial experience is good, the drug could be considered for inclusion in WHO’s Essential Drugs List, and would then likely be used widely by malaria control programmes.

NEW AND IMPROVED EPIDEMIOLOGICAL TOOLS

FILARIASIS: Rapid assessment procedures for *Loa loa*

There is a need to identify areas where people have very high loads of *Loa loa* worms, especially in areas where loiasis co-exists with onchocerciasis, because of the high risk of serious adverse reactions to ivermectin treatment in patients with a high intensity of *L. loa* infection. This information is urgently needed to allow planning for mass treatment campaigns with ivermectin for onchocerciasis in central African countries where *L. loa* may be endemic.

Partly based on earlier work supported by TDR, the threshold for *L. loa* endemicity above which the risk of severe reactions becomes too high for routine treatment with ivermectin has provisionally been set at 20% prevalence of microfilariae (mf), or 5% prevalence of high intensity (more than 8000mf/ml) of *L. loa* infection. A study under way in Cameroon and Nigeria will determine whether a rapid assessment procedure for *L. loa*, based on history of eye worm or Calabar swelling, will effectively identify villages with a prevalence above the stipulated level. The study will also help to better quantify the relationship between prevalence and intensity of *L. loa* infection. History of eye worm (whether worms moving along the white of the lower part of the eye have ever been experienced) or Calabar swell-
ing (whether swellings under the skin which change position or disappear have ever been experienced) will be gleaned by interviews at both community and individual level.

**FILARIASIS: Rapid mapping methods**

The method of Rapid Assessment of the Geographical Distribution of Filariasis (RAGFIL) was developed by TDR, as reported in the Fourteenth TDR Programme Report (1997-1998). RAGFIL is based on a 50 km grid sampling technique. In the multicountry study completed in 1999 and carried out in Ghana, India, Myanmar and the United Republic of Tanzania, the prevalence of lymphatic filariasis was estimated by hydrocele examination or antigen testing using the ICT test (an immunochromatographic whole blood card test). The study showed RAGFIL to be effective for clarifying the distribution of Bancroftian filariasis and mapping the approximate contours of levels of endemicity, including areas of very low or no risk. The antigen test (ICT) was found to be a better diagnostic test than clinical examination for hydrocele by health workers. The results from India were less clear than in the other countries. RAGFIL was recommended for use in Africa, with fine-tuning for the first large-scale applications.

In the meantime however, other ideas had emerged about mapping of filariasis, based on use of the implementation unit – the health administrative unit within which residents would receive mass treatment. A standard method for mapping filariasis in Africa has now been agreed upon which combines the strongest elements of the different ideas, including use of the implementation unit and the spatial sampling and analysis approach of RAGFIL. The mapping of filariasis in Africa will be implemented in phases. The first phase has started in five West African countries and Tanzania. It is coordinated by the programme to eliminate lymphatic filariasis at WHO with technical support from TDR. Four countries have been mapped, showing a huge lymphatic filariasis focus covering North Ghana and Togo and nearly all of Burkina Faso. On the basis of these results, national plans for lymphatic filariasis elimination have now been developed by each of the four countries concerned.
SCHISTOSOMIASIS: Remote sensing and geographical information systems (GIS)

In collaboration with other UN agencies, such as the Food and Agriculture Organization (FAO) and regular budget WHO programmes, TDR promotes research in the field of epidemiology using remote sensing by earth-observing satellites and geographical information systems to produce maps showing the real risk for health. There has been good progress in this area, promising a rapidly improving database of the risk for schistosomiasis in the world. At a team residency in Bellagio, Italy, sponsored by the Rockefeller Foundation in April 2000, an organizational plan was conceived to create a global network of collaborating health workers and earth scientists dedicated to the development of computer-based models that can be used for improved control programmes for schistosomiasis and other snail-borne diseases of medical and veterinary importance. The proceedings are published as a special issue of Acta tropica.13

GIS mapping in China